OVERVIEW OF THE PATHOGENESIS OF ASTHMA

An overview of current insights into the pathophysiology of asthma is presented here in order to provide a context in which recommendations regarding asthma treatment were made for the *Expert Panel Report Update.*

The working definition of asthma, as proposed in the *Expert Panel Report* in 1997 (page 3)—

> *Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli (NHLBI 1997).*

—continues to capture the features of asthma and underscores the importance of airway inflammation to the pathogenesis, pathophysiology, and treatment of this disease. Important additions to this definition include recent observations that reversibility may be incomplete in some patients with asthma, and other individuals with features of chronic bronchitis may manifest some degree of reversibility in airflow obstruction (Bousquet J. et al. 2000). Nonetheless, the study of asthma pathogenesis and its treatment continues to focus on inflammation as a target to control and regulate airflow obstruction and the resulting symptoms.

Recent studies have begun to categorize airway inflammation into phases, which although somewhat arbitrary in demarcation, provide insights into the possible progression of the disease as well as its management. Acute symptoms of asthma usually arise from bronchospasm and require and respond to bronchodilator therapy. Acute and chronic inflammation can affect not only the airway caliber and airflow but also underlying bronchial hyperresponsiveness, which results in susceptibility to bronchospasm. Treatment with anti-inflammatory drugs can, to a large extent, reverse some of these processes; however, the successful response to therapy often requires weeks to achieve and, in some situations, may be incomplete. Finally, some patients may have persistent airflow limitations for which no current therapy has been found to be effective. Therefore, the paradigm of asthma has been expanded from bronchospasm and airway inflammation to include airway remodeling in some patients. The concept that asthma may be a continuum of these processes that can lead to moderate and severe persistent disease is of critical importance to understanding this disease's pathogenesis and pathophysiology. As these questions undergo a constant evaluation, current treatment recommendations also must be reassessed.

Inflammation of Asthma

Airway inflammation in asthma is found in patients with mild, moderate, and severe disease. Although there are some universal features of this inflammatory response in the airway, the specifics of the bronchial reaction show variations, which are dependent upon the disease's severity, treatment, and duration. Infiltration of the airway by inflammatory cells such as activated lymphocytes and eosinophils, denudation of the epithelium, deposition of collagen in the subbasement membrane area, and mast cell degranulation are often, but not always, features of mild or moderate persistent asthma. In fatal disease and severe persistent asthma, other conditions occur, such as occlusion of the bronchial lumen by mucus, hyperplasia and hypertrophy of the bronchial smooth muscle, and goblet cell hyperplasia.

The cellular profile of inflammation in asthma provides evidence for the nature of the immune reaction of injury and remodeling or repair, the potential mechanisms by which such responses occur, the resulting alteration in physiology, and the possible therapeutic targets necessary to regulate, reverse, or prevent such events. IgE antibodies have been found to have a relationship to the severity of asthma and the airway's early response to allergens. The ability to synthesize IgE antibodies to environmental allergens (i.e., atopy) remains a major risk factor in asthma pathogenesis. Synthesized IgE binds to mast cells and basophils via high-affinity IgE receptors, and the bridging of these attached molecules signals the cells to release preformed and newly generated mediators, including histamine and cysteinyl leukotrienes, to rapidly contract airway smooth muscle. In addition, the mast cell can produce a variety of cytokines, including interleukin (IL)-1, -2, -3, -4, and -5 along with granulocyte-macrophage colony-stimulating factor, interferon (IFN)-γ, and tumor necrosis factor-α. The generation of these pro-inflammatory proteins suggests that mast cells can contribute to both acute and chronic inflammation.

Eosinophilic infiltration of the airway remains a consistent feature of acute inflammation and also is found in mucosal airway tissue from many patients with chronic, persistent asthma. The granule proteins of the mature eosinophil are sources of inflammatory mediators, including major basic protein, which can injure airway epithelium, enhance bronchial responsiveness, and affect the regulation of acetylcholine release. In addition, the eosinophil can release cysteinyl leukotrienes, such as C_4, to contract airway smooth muscle. The production of eosinophils and their release from the bone marrow are regulated by IL-5. Migration of these cells to the airway involves an interaction of eosinophil surface-bound integrins, β_1 and β_2, with endothelial cell and matrix tissue counterligands. Finally, recently identified families of

chemokines (RANTES) eotaxin, and macrophage inflammatory protein-1α, participate in the migration of these cells to the airway. Although the eosinophil is a feature of asthma pathology that is known to be affected by anti-inflammatory therapy in a manner that improves airway physiology, its precise role in the pathophysiology of asthma is still under investigation.

An Imbalance Between Th1 and Th2 in the Origins of Asthma

The role of lymphocytes in the inception and progression of asthma continues to be of considerable importance. Since the 1997 Expert Panel Report, there has been interest in the idea that an imbalance in T-helper (Th) 1 and Th2 cytokines may help explain and even predict the subsequent development of asthma. Airway inflammation in asthma may represent a loss of normal balance between two "opposing" populations of Th lymphocytes. Two types of Th lymphocytes have been characterized: Th1 and Th2. Th1 cells produce IL-2 and IFN-γ, which are critical in cellular defense mechanisms in response to infection. Th2, in contrast, generates a family of cytokines (IL-4, -5, -6, -9, and -13) that can mediate allergic inflammation. The current "hygiene hypothesis" of asthma illustrates how this cytokine imbalance may explain some of the dramatic increases in asthma prevalence in Westernized countries. This hypothesis is based on the assumption that the immune system of the newly born is skewed towards Th2 cytokine generation. Following birth, environmental stimuli such as infections will activate Th1 responses and bring the Th1/Th2 relationship to an appropriate balance. There is evidence that the incidence of asthma is reduced in association with certain infections (*M. tuberculosis,* measles, or hepatitis A); exposure to other children (e.g., presence of older siblings and early enrollment in childcare); and less frequent use of antibiotics. Furthermore, the absence of these lifestyle events is associated with the persistence of a Th2 cytokine pattern. Under these conditions, the genetic background of the child, with a cytokine imbalance toward Th2, will set the stage to promote the production of IgE antibody to key environmental antigens, such as house dust mite, cockroach, *Alternaria,* and possibly cat. Therefore, a gene-by-environment interaction occurs in which the susceptible host is exposed to environmental factors that are capable of generating IgE, and sensitization occurs. Precisely why the airways of some individuals are susceptible to these allergic events is not established.

There also appears to be a reciprocal interaction between the two subpopulations in which Th1 cytokines can inhibit Th2 generation and vice versa. Allergic inflammation may be the result of an excessive expression of Th2 cytokines. Alternately, the possibility that the loss of normal immune balance arises from a cytokine dysregulation in which Th1 activity in asthma is diminished has been suggested in recent studies. The focus and actions of cytokines and chemokines to regulate and activate the inflammatory profile in asthma has provided ongoing and new insight into the pattern of airway injury that may lead to new therapeutic targets.

Because of the importance of IgE to the pathogenesis of allergic diseases and inflammation, the development of humanized monoclonal antibodies has become a possible treatment. Early studies in asthma have indicated that this approach can reduce serum IgE, inhibit the immediate and late airway response to inhaled antigen, and allow for a withdrawal of inhaled corticosteroids without deterioration in lung function or precipitation of an asthma exacerbation. The findings of anti-IgE monoclonal antibody therapy support the importance of IgE-mediated responses in asthma and suggest that IgE-regulated processes may encompass processes that influence inflammation other than mast-cell-dependent responses.

In addition, monoclonal antibodies against IL-5 recently have been tested in asthma. Anti-IL-5 has reduced circulating concentrations of eosinophils and their presence in sputum. However, despite the reduction (but not elimination) of eosinophils, there was no change in the development of the late-phase response to an inhaled antigen. These preliminary studies have raised questions about the specific role of IL-5 in mechanisms of airflow obstruction and of eosinophils in the pathophysiology of asthma. It appears to be an omnipresent cell in asthma, but how it participates in the disease process is not yet clear.

A soluble IL-4 receptor (IL-4R) has been developed for inhaled administration. This molecule acts as a decoy and is capable of binding to IL-4 and thus acting as an antagonist for that molecule. Although early studies that administered nebulized IL-4R showed that inhaled corticosteroid doses can be reduced without a loss of asthma control or lung function, subsequent trials with this molecule have failed to demonstrate effectiveness in asthma control.

A number of lessons can be learned from these early studies directed toward a single cytokine. Although modification of features of allergic inflammation can be seen in animals with genes that have "knocked out" selected cytokines, similar benefits have not necessarily been seen in human asthma. These findings underscore the relevancy of multiple factors regulating inflammation in asthma and the redundancy of these processes. Moreover, these clinical studies in human asthma also serve to indicate that phenotypes of asthma exist and that these phenotypes may have very specific patterns of inflammation. Nonetheless, as more clinical trials with modifiers of inflammation in asthma are performed, it is likely that a more comprehensive insight into the mechanisms of this disease will occur.

In summary, recent evidence continues to underscore the importance of immune factors in the development of asthma and resulting inflammation processes. Insight into the mechanisms of these processes will be important for future therapy. In the meantime, asthma therapy continues to focus on controlling underlying airway inflammation.

REFERENCES

Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodeling. *Am J Respir Crit Care Med* 2000 May;161(5):1720–45.